UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,653	11/16/2006	Wei Cheng	05-937-B5	5425

20306 7590 11/16/2009

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
11/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,653	CHENG ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-20,29,34,35,37 and 39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13-20, 29, 34 and 35* is/are allowed.

6)☒ Claim(s) *37 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Applicants title their response to a "Restriction Requirement," but, as this application was filed under 35 USC 371, this is properly a Lack of Unity requirement and those rules of procedure apply.

Applicants' election with traverse of Group II in the Response filed on 07-24-2009 is acknowledged. Claims 13-20, 29, 34, 35, 37 and 39-43 are under examination on their merits.

Applicants traverse the Lack of Unity because claim 1 is generic and refer to MPEP 803.02 and 809. However, Chapter 800 of the Manual of Patent Examining Procedure relate to applications filed under 35 USC 111. Applicants rely on *In re Harnisch*, 206 USPQ 300 (CCPA 1980), *In re Weber, et al.*, 198 USPQ 328 (CCPA 1978), *Ex parte Brouard, et al.*, 201 USPQ 538 (BPAI 1976), and *Ex parte Hozumi*, 3 USPQ2d 1059 (BPAI 1984), however all of these cases related to Restriction Requirements not Lack of Unity. For all reasons advanced in the Lack of Unity in the Office Action of 03-24-2009, this Lack of Unity is seen to be proper and is maintained.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Abstract

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Applicants are requested to include a structural formula of the claimed compounds as an aid to future researchers.

Complete revision of the content of the abstract is required on a separate sheet.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The specification does not reasonably enable a method using a compound of claim 13 to modulate *in vivo* activity of p70S6K (claim 37), inhibit p70S6K (claim 39), treat disease or disorder associated with uncontrolled, abnormal or unwanted cellular activities (claim 40), screen for a p70S6 kinase modulator (claim 41), inhibit cell proliferative activity (claim 41) or inhibit abnormal cell metabolic activity (claim 43).

The specification asserts the claimed compounds inhibit, regulate or modulate kinase or p70S6K activity and are therefor of value in the above recited conditions, for

which insufficient enablement is provided. To "modulate" may mean "to adjust or adapt to a certain proportion; regulate or temper, or "to alter or regulate so as to achieve accuracy or conform to a standard." However, there is no indication of the proportion or standard to which the p70S6K is to be modulated. Does modulate mean to increase or to decrease *in vivo* p70S6K activity? The specification at ¶ [0097] states: "Another aspect of the invention is the method according to paragraph [0059], wherein modulating the *in vivo* activity of p70S6K comprises inhibition of p70S6K." However, as stated, this is only one aspect of the invention and fails to teach how to obtain the degree, conditions or situations of inhibition intended.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, 66 FR 1092-1099 (2001), emphasizing "a claimed invention must have a specific and substantial utility." MPEP 2163, *et. seq*. This disclosure is insufficient to enable the claimed methods based on the disclosed PDE2 inhibition.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover methods using substituted pyrimidine compounds.

(b) Scope of the conditions covered. The claims cover methods to treat above conditions said to be responsive to inhibition, regulation or modulation of p70S6K kinase signal transduction.

Modulate p70S6K activity *in vivo*. p70 ribosomal protein S6 kinase (p70S6K) participates in protein synthesis control and activates in response to hormones, mitogens and nutrients. p70S6K phosphorylates the 40S ribosomal protein S6, which is involved in translation of certain mRNAs, the 5'-TOP mRNAs encoding

ribosomal proteins and elongation factors. p70S6K is activated by insulin in muscle, but not in hepatocytes. In these cells, p70S6K is activated by amino acids like glutamine and leucine, which act synergistically. However, crosstalk between insulin and amino acids can be demonstrated with leucine, which enhances insulin signaling towards p70S6K in many cell types, including hepatocytes.

The mechanism of p70S6K activation involves a complex sequence of multiple serine/threonine phosphorylations catalyzed by several protein kinases. One of these is the mammalian target of rapamycin (mTOR), which phosphorylates p70S6K on Thr389 and is inhibited by the immunosuppressant rapamycin. Phosphorylation of this site correlates with kinase activity. mTOR may also phosphorylate and thereby inactivate a protein phosphatase that in turn inactivates p70S6K. The amino-acid signaling pathway leading to p70S6K activation may comprise inhibition of protein phosphatase. Whatever the activation mechanism of p70S6K by mTOR, the latter plays an essential role, because p70S6K activation caused by almost all stimuli is inhibited by rapamycin. Phosphorylation of Ser411, Thr421 and Ser424, which are within a Ser-Pro rich region located in the autoinhibitory domain, is also thought to modulate p70S6K activity. In response to insulin, 3-phosphoinositide-dependent protein kinase (PDK1) is directly involved in p70S6K activation. Target phosphorylation site for PDK1 is Thr229 in the p70S6K catalytic domain.

Acetyl-CoA carboxylase (ACC) is a regulatory enzyme in fatty acid synthesis. In liver cells ACC activation is correlated with cell swelling induced by amino acids cotransported with Na^+ or by hypotonic medium. ACC activity is controlled by various

mechanisms, including changes in the degree of polymerization, allosteric regulation by citrate and glutamate and covalent modification by phosphorylation/dephosphorylation. The active form is generally assumed to be dephosphorylated, although phosphorylation has been invoked to explain ACC activation by insulin in adipocytes.

Under stress conditions, such as anoxia or inhibition of mitochondrial oxidative phosphorylation, ATP balance becomes negative and the AMP/ATP ratio increases. This leads to AMP-activated protein kinase (AMPK) activation, which functions as a metabolic master switch and inhibits anabolic processes, preserving ATP. ACC is phosphorylated *in vitro* by AMPK on Ser79, Ser1200 and Ser1250, the phosphorylation of Ser79 being responsible for inactivation. AMPK-inactivated ACC can be reactivated by a glutamate-dependent type-2A protein phosphatase (GAPP), which dephosphorylates a synthetic peptide encompassing the Ser79 phosphorylation site for AMPK in ACC. In hepatocytes the activation ACC state is expected to result from balance between GAPP and AMPK activities, although involvement of other protein kinase or phosphatases has not been ruled out.

Because ACC and p70S6K display a similar and parallel pattern of activation in hepatocytes incubated with glutamine, the question arises whether there is also a common mechanism for inactivation. It is indeed expected that ACC and p70S6K, which control energy-consuming biosynthetic pathways, are less active when ATP supply becomes limiting. The effect of different AMPK activators and the effect of protein phosphatase inhibitors the amino-acid-induced ACC and p70S6K activation were examined in freshly prepared rat hepatocytes. Results show that ACC and

p70S6K activation depend on protein phosphatase and both enzymes may be inactivated under conditions leading to AMPK activation.

Kinases (phosphotransferase) are enzyme types that transfer phosphate groups from high-energy donor molecules, e.g., ATP, to specific target molecules (substrates); the process is termed *phosphorylation.* An enzyme that *removes* phosphate groups from targets is known as a phosphatase. One of the largest kinase groups are protein kinases, which act on and modify activity of specific proteins, transmit signals and control complex cell processes. Up to 518 different human kinases have been identified. Various other kinases act on small molecules (lipids, carbohydrates, amino acids, nucleotides, and more), either for signaling or to prime them for biochemical reactions in metabolism.

Uncontrolled, abnormal or unwanted cellular activities. It is not possible to know what is intended by "diseases or disorders associated with uncontrolled, abnormal and/or unwanted cellular activities.

- "In *polycythemia vera*, uncontrolled and rapid cellular reproduction and maturation cause proliferation or hyperplasia of all bone marrow cells. The cause of such uncontrolled cellular activity is probably due to a multipotential stemcell defect." Do the methods of this invention treat *polycythemia vera?*
- A genetic predisposition with inadequate immune responses and uncontrolled cellular activity may make some women more susceptible to cervical cancer. Do the methods of this invention treat cervical cancer?

- Dreams are caused mostly by uncontrolled cellular activity. Do the methods of this invention alleviate treat uncontrolled, abnormal and/or unwanted dreams?
- A benign tumor is any abnormal cellular growth that remains confined to one area, is not cancerous and does not spread to distant body areas. Do the methods of this invention treat benign tumors?
- Abnormal cellular activity is often one predisposing factor for human osteosarcoma. Do the methods of this invention treat osteosarcoma?
- Inflammation and gene expression can be considered unwanted cellular activities. Do these inventive methods treat inflammation and gene expression?

Inhibition of cell proliferative activity. Mild intracellular redox imbalance inhibits cell proliferation independent of reactive oxygen species generation. Inhibition of the growth of hepatocellular carcinoma has been attributed to a decrease of cell proliferative activity. Indole-3-carbinol selectively inhibits cell proliferative activity induced by estradiol in responsive human breast cancer cells and phosphorylation of the estrogen receptor. CD54 and CD106 are involved in the ability of follicular dendritic cells to inhibit T-cell proliferative responses. Conjugated linoleic acid may act by antioxidant mechanisms, prooxidant cytotoxicity, inhibition of nucleotide and protein synthesis, reduction of cell proliferative activity and inhibition of both DNA-adduct formation and carcinogen activation. In male Syrian hamsters, stress influences epidermal cell proliferative activity and sebaceous gland activity.

Inhibition of abnormal cell metabolic activity. Increasing oxygen delivery to the myocardium so that the mitochondria can make more ATP via aerobic

mechanisms and/or by decreasing heart rate and arterial blood pressure and thus, the rate of ATP breakdown by tissue, are pharmacologic therapies aimed at reducing abnormal cell metabolism to treat chronic stable angina.

The specification fails to identify treatment results with methods of this invention and how to recognize such results. Each of the above conditions has various symptoms and there is no indication of which specific symptoms are alleviated.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics Corp., 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claim.
4. **State of the prior art:** The art indicates the need for undue experimentation.

The anti-proliferative effects of sirolimus (Rapamycin, a p70S6K inhibitor) may have a role in treating cancer, but Rapamycin shows no effect on its own. Doxorubicin and sirolimus combination therapy has been shown to drive AKT-positive lymphomas into remission in mice. Bcl-2-positive lymphomas were completely resistant to sirolimus therapy; eIF4E expressing lymphomas are not sensitive to sirolimus. As with all immunosuppressive medications, Rapamycin decreases the body's inherent anti-cancer activity and allows some cancers to proliferate, which would otherwise have been naturally destroyed. Wikipedia, Sirolimus (already of record).

Sawyers, Nature Reviews – Cancer (already of record), studying rapamycin use in renal cancer treatment, detected that rapamycin delivery to tumor cells is impaired in some patients and concluded, "This trial shows the importance of investigating drug delivery to tumour cells and target modulation in patients to guide future clinical development of targeted agents. Further study of rapamycin in PTEN-deficient glioblastoma is warranted."

Ability of any and all kinases or a p70S6K inhibitor to effectively treat all conditions encompassed by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests of all recited conditions the claims encompass. Applicants do not provide competent evidence that the instantly disclosed tests are highly predictive for all uses covered embraced by claim language for all intended hosts.

6. **Skill of those in the art:** Wikipedia and Sawyers call into question treatment with the claimed methods and confirm the need for additional research.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, one skilled in the pharmaceutical arts would have an undue burden to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles above, indicates the requirement for undue experimentation. The ability of an agent that treats all conditions construed by the claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claim. Undue experimentation will be required to practice Applicants' invention.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all of the embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." Here, the claims at issue cover many embodiments and do not enable any of them.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the embodiments. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." Here, the claims at issue cover many embodiments and do not enable any of them.

Response to Remarks of 07-24-2009

At page 45 of the Remarks of 07-27-2009, Applicants state,"...these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values ..." If Applicants now intend that "modulating" is intended to be given the specific interpretation of "inhibiting," the claims must be so amended and support for such amendment in the specification must be identified.

The 07-27-2009 Remarks, page 45, state,"...Applicants assert that the breadth of the claims is very specific towards modulating, or inhibiting, *in vivo* activity of p70S6k." Does this mean "modulating" is equated with "inhibiting" or that they are alternatives for each other? This cannot be true, because "to modulate" means "to adjust or adapt to a certain proportion; regulate or temper," or "to alter or regulate to achieve accuracy or conform to a standard," while "to inhibit" means "to prohibit from doing something; to hold in check, to restrain; to discourage from free or spontaneous activity."

Wikipedia and Sawyers both show that, even granted that the compounds may modulate or inhibit p70S6k, this alone does not define a method of using those compounds for a presently effective utility. Wikipedia discusses some of the deleterious side effects of p70S6k for Rapamycin, a known p70S6k inhibitor. Sawyers revealed that rapamycin delivery to tumor cells is impaired in some patients.

With another known p70S6k inhibitor, hamartin, Gomez-Cambronero, et al., J. Immunol., 2003, 6846-6855, reported that "hamartin transduced into cells as active protein, interfered with GM-CSF-dependent migration and attenuated p70S6k phosphorylation." Thus, stating that a compound will modulate or inhibit p70S6k *in vitro*

does not teach how to use that compound for a presently available utility, because of the deleterious effects to be expected.

Applicants assert that claim 40 relates to "a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering" in a mammal. However, Applicants' response is totally silent on whether the claimed methods will treat *polycythemia vera,* cervical cancer, uncontrolled, abnormal and/or unwanted dreams, benign tumors, osteosarcoma, inflammation or gene expression, all of which are diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities in a mammal. Note that both *Sitrick v. Dreamworks LLC*, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) and *Automotive Tech. Int'l. v. BMW of N. America, Inc.*, 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) stand for the proposition that, where the claims at issue cover many embodiments, the specification must enable all of them.

Applicants state that a p70S6k role in tumor cell proliferation and cell protection from apoptosis is supported by p70S6k participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues, citing articles by Pene, Miyakawa, Le and Peralba. These articles are not presently of record. If Applicants wish to have these references considered in the file of this application and listed on the cover of any patent that may issue from this application, they must cite these documents in an Information Disclosure Statement and provide copies thereof.

- "Pene" appears to be Pene, et al., "Role of the phosphatidylinositol 3-kinase/Akt and mTOR/P70S6-kinase pathways in the proliferation and apoptosis in multiple

myeloma," Oncogene (2002), 21, 6587-6597. If Applicants intend that their claimed methods treat multiple myeloma, they are invited to present such evidence.

- "Miyakawa" appears to be Miyakawa, et al., "Increased Expression of Phosphorylated p70S6 Kinase and Akt in Papillary Thyroid Cancer Tissues," Endocrine J., 2003, 50(1), 77-83. If Applicants intend that their claimed methods treat papillary thyroid cancer, they are invited to present such evidence.
- "Le" appears to be Le, et al., "Paclitaxel induces inactivation of p70 S6 kinase and phosphorylation of Thr^{421} and Ser^{424} via multiple signaling pathways in mitosis," Oncogene (2003), 22, 484-497. If Applicants intend the claimed methods treat breast and ovarian cancer, as Le suggests, they are invited to present such evidence.
- "Peralba" appears to be Peralba, et al., "Pharmacodynamic Evaluation of CCI-779, an Inhibitor of mTOR in Cancer Patients," Clinical Cancer Research, 9, 2887-2892, Aug. 1, 2003. If Applicants intend that their claimed methods treat cancer, as Peralba suggests, they are invited to present such evidence.

Claim 41 fails to teach how to use the inventive compounds to screen for a p70S6k kinase modulator. The candidate agent is undefined, the method of combining a claim 13 compound and a candidate agent is undefined, possible effects to be noted in a candidate agent are undefined, and the potential activity of the p70S6k kinase is undefined. The indefiniteness of the term "modulator" has been considered above.

Claim 42 fails to teach how to inhibit proliferative activity in a cell with a claim 13 compound. The claim fails to define to whom or to what the compound is administered. The cell type is undefined. To the extent that the claim construes both *in vivo* and *in*

vitro inhibition and administration, there is no indication that *in vitro* results predict *in vivo* inhibition. Note that Buset, et al., Canc. Res. 46, 5426-5430, 10-1986, showed that certain patient biopsies, growth inhibited by CaCl2 *in vitro,* were taken from patients who did not subsequently respond in an *in vivo* trial, showing that *in vitro* results are not necessarily predictive of *in vivo* inhibition. In *Abbott Labs. v. Sandoz Inc.*, 89 USPQ2d 1161, 1169, (Fed. Cir. 2008), the parties agreed "*in vitro* data are not predictably transferable to *in vivo* conditions." See *Alza Corp. v. Mylan Labs.*, 80 USPQ2d 1001 (Fed. Cir. 2006) ("Alza's evidence of *in vitro* dissolution rates is irrelevant absent evidence demonstrating that the *in vitro* system is a good model of actual *in vivo* behavior.").

Claim 43 fails to teach how to inhibit abnormal metabolic activity in a cell with a claim 13 compound. "Abnormal metabolic activity" is inclusive of such diverse conditions as GPi efferent projections in parkinsonism (Eidelberg, et al., Brain (1997), 120, 1315-1324), recurrent and metastatic adrenocortical carcinoma (Mackie, et al., J. Clinical Endocrinology & Metabolism 91(7):2665-2671, 2006), and human breast cancer (McDermott, et al., Brit. J. Surgery, Vol. 77, #10, 1179-1182, 2005). If Applicants intend that the method of this claim treats such conditions, they are invited to present corroborating data. The claim fails to define to whom or to what the compound is administered. The type of cell is undefined. To the extent that the claim construes both *in vivo* and *in vitro* inhibition and administration, there is no indication that *in vitro* results are predictive of *in vivo* inhibition. See Buset cited and discussed above. See also the discussion of *Abbott Labs. v. Sandoz Inc.* and of *Alza Corp. v. Mylan Labs.* above.

Accordingly, claims 37 and 39-43 fail to comply with the enablement requirement of 35 U.S.C. 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37 and 39-43: The recitation of modulation of *in vivo* activity of p70S6K kinase, inhibiting p70S6K, treating any disease or disorder associated with uncontrolled, abnormal or unwanted cellular activities, screening for a p70S6 kinase modulator, inhibiting cell proliferative activity or inhibiting abnormal cell metabolic activity fail to particularly point out and distinctly claim the intended subject matter. It is not possible to determine exactly what these terms encompass and define.

Modulate p70S6K activity *in vivo*. To "modulate" may mean "to adjust or adapt to a certain proportion; regulate or temper," or "to alter or regulate so as to achieve accuracy or conform to a standard." However, there is no indication of the proportion or standard to which the p70S6K is to be modulated. Does modulate mean to increase or to decrease *in vivo* p70S6K activity? The specification at ¶ [0097] states: "Another aspect of the invention is the method according to paragraph [0059], wherein modulating the *in vivo* activity of p70S6K comprises inhibition of p70S6K." However, as

stated, this is only one aspect of the invention and fails to define the degree, conditions or situations for which inhibition is intended.

p70S6K participates in protein synthesis control and activates in response to hormones, mitogens and nutrients. It phosphorylates the 40S ribosomal protein S6, which is involved in translation of certain mRNAs, the 5'-TOP mRNAs encoding ribosomal proteins and elongation factors. p70S6K is activated by insulin in muscle, but not in hepatocytes. In these cells, p70S6K is activated by amino acids like glutamine and leucine, which act synergistically. However, crosstalk between insulin and amino acids can be demonstrated with leucine, which enhances insulin signaling towards p70S6K in many cell types, including hepatocytes.

p70S6K activation mechanism involves a complex sequence of multiple serine-threonine phosphorylations catalyzed by several protein kinases. One of these is the mammalian target of rapamycin (mTOR), which phosphorylates p70S6K on Thr389 and is inhibited by rapamycin. Phosphorylation of this site correlates with kinase activity. mTOR may also phosphorylate and inactivate a protein phosphatase that also inactivates p70S6K. The amino-acid signaling pathway leading to p70S6K activation may comprise protein phosphatase inhibition. Whatever the activation mechanism of p70S6K by mTOR, the latter plays an essential role, because rapamycin inhibits almost all stimuli caused by p70S6K activation. Phosphorylation of Ser411, Thr421 and Ser424, which are within a Ser-Pro rich region located in the autoinhibitory domain, is also thought to modulate p70S6K activity. In response to insulin, 3-phosphoinositide-

dependent protein kinase (PDK1) is directly involved in p70S6K activation. Target phosphorylation site for PDK1 is Thr229 in the p70S6K catalytic domain.

Acetyl-CoA carboxylase (ACC) is a regulatory enzyme in fatty acid synthesis. In liver cells ACC activation is correlated with cell swelling induced by amino acids cotransported with Na^+ or by hypotonic medium. ACC activity is controlled by various mechanisms, including changes in the degree of polymerization, allosteric regulation by citrate and glutamate and covalent modification by phosphorylation/dephosphor-ylation. The active form is generally assumed to be dephosphorylated, although phosphorylation has been invoked to explain ACC activation by insulin in adipocytes.

Under stress conditions, e.g., anoxia, mitochondrial oxidative phosphorylation inhibition, ATP balance becomes negative and AMP/ATP ratio increases. This leads to AMP-activated protein kinase (AMPK) activation, which functions as a metabolic master switch and inhibits anabolic processes, preserving ATP. AMPK on Ser79, Ser1200 and Ser1250 phosphorylate ACC *in vitro*, Ser79 phosphorylation being responsible for inact-ivation. AMPK-inactivated ACC can be reactivated by a glutamate-dependent type-2A protein phosphatase (GAPP), which dephosphorylates a synthetic peptide encompass-sing the Ser79 phosphorylation site for AMPK in ACC. In hepatocytes, the activation ACC state is expected to result from balance between GAPP and AMPK activities, although other protein kinase or phosphatase involvement has not been ruled out.

Because ACC and p70S6K display a similar and parallel activation pattern in hepatocytes incubated with glutamine, the question arises whether there is also a common inactivation mechanism. It is indeed expected that ACC and p70S6K, which

control energy-consuming biosynthetic pathways, are less active when ATP supply becomes limiting. The effect of different AMPK activators and the effect of protein phosphatase inhibitors on the amino-acid-induced ACC and p70S6K activation were examined in freshly prepared rat hepatocytes. Results show that ACC and p70S6K activation depend on protein phosphatase and both enzymes may be inactivated under conditions leading to AMPK activation.

Kinases (phosphotransferase) are enzyme types that transfer phosphate groups from high-energy donor molecules, e.g., ATP, to specific target molecules (substrates) in a process of *phosphorylation.* An enzyme that *removes* phosphate groups from targets is a phosphatase. One of the largest kinase groups are protein kinases, which act on and modify specific protein activity, transmit signals and control complex cell processes. Up to 518 different human kinases have been identified. Various other kinases act on small molecules (lipids, carbohydrates, amino acids, nucleotides, and more), either for signaling or to prime them for biochemical reactions in metabolism.

Uncontrolled, abnormal or unwanted cellular activities. It is not known what is meant by this term as it does not appear to be a term with a defined meaning. For example, in *polycythemia vera*, uncontrolled and rapid cellular reproduction and maturation cause proliferation or hyperplasia of all bone marrow cells. The cause of such uncontrolled cellular activity is probably due to a multipotential stemcell defect. A genetic predisposition with inadequate immune responses and uncontrolled cellular activity may make some women more susceptible to cervical cancer. Dreams are caused mostly by uncontrolled cellular activity. A benign tumor is any abnormal cellular growth that rem-

ains confined to one area, is not cancerous and does not spread to distant body areas. Abnormal cellular activity is often one predisposing factor for human osteosarcoma. Inflammation and gene expression can also be considered unwanted cellular activities.

Cell proliferative activity inhibition. It is not known what this term means, as it does not appear to have a defined meaning. Mild intracellular redox imbalance inhibits cell proliferation independent of reactive oxygen species generation. Hepatocellular carcinoma growth inhibition has been attributed to cell proliferative activity decrease. Indole-3-carbinol selectively inhibits estradiol-induced cell proliferative activity in responsive human breast cancer cells and estrogen receptor phosphorylation. CD54 and CD106 are involved in ability of follicular dendritic cells to inhibit T-cell proliferative responses. Conjugated linoleic acid may act by antioxidant mechanisms, prooxidant cytotoxicity, nucleotide and protein synthesis inhibition, cell proliferative activity reduction and inhibition of both DNA-adduct formation and carcinogen activation. In male Syrian hamsters, stress influences epidermal cell proliferative activity and sebaceous gland activity.

Inhibition of abnormal cell metabolic activity. It is not known what is meant by this term as it does not appear to be a term with a defined meaning. Increasing oxygen delivery to the myocardium so that the mitochondria can make more ATP via aerobic mechanisms and/or by decreasing heart rate and arterial blood pressure and thus, the rate of ATP breakdown by tissue, are pharmacologic therapies aimed at reducing abnormal cell metabolism to treat chronic stable angina.

In claim 41, the candidate agent is undefined, the method of combining a claim 13 compound and a candidate agent is undefined, the possible effects to be noted in a

candidate agent are undefined, and potential activity of the p70S6k kinase is undefined. The indefiniteness of the term "modulator" has been considered above.

Claim 42 fails to define to whom or to what the compound is administered. The type of cell is undefined. The claim fails to define if administration is *in vivo* or *in vitro.*

In claim 43, "abnormal metabolic activity" is undefined; it can be inclusive of such diverse conditions as GPi efferent projections in parkinsonism (Eidelberg, et al., cited above), recurrent and metastatic adrenocortical carcinoma (Mackie, et al., cited above), and human breast cancer (McDermott, et al., cited above). The claim fails to define to whom or to what the compound is administered. The type of cell is undefined. The claim fails to define if administration is *in vivo* or *in vitro.*

Response to Remarks of 07-24-2009

At page 45 of the Remarks of 07-27-2009, Applicants state,"…these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values …" If Applicants now intend that "modulating" is meant to be given the specific interpretation of "inhibiting," the claims must be so amended and support for such amendment in the specification must be identified.

At page 49, Applicants assert that claims 37 and 39 particularly point out and distinctly claim a method to modulate or inhibit *in vivo* activity of a p70S6K kinase, as recited therein. The discussion above well documents reasons that recitation of such a method fails to meet the requirements of 35 USC 112, paragraph 2, and that discussion is repeated here. Applicants' remarks make no comment on the above discussion.

Regarding claim 40, Applicants assert that this claim particularly points out and distinctly claims a method of treating diseases or disorders associated with uncontrolled, abnormal and/or unwanted cellular activities. The discussion above documents reasons that recitation of such a method fails to meet the 35 USC 112, paragraph 2, requirements and that discussion is repeated here. Applicants' remarks completely ignore the above discussion. The newly cited articles by Pene, Miyakawa, Le and Peralba do not supply for the deficiencies of the claims and the specification.

Applicants' Pene citation appears to assert that the claimed method will treat multiple myeloma. If this is Applicants' intention, they must present such evidence. Applicants' Miyakawa citation appears to assert that the claimed method will treat papillary thyroid cancer. If this is Applicants' intention, they must present evidence. Applicants' Le citation appears to assert that the claimed method will treat breast and ovarian cancer. If this is Applicants' intention, they must present such evidence. Applicants' citation of Peralba appears to assert that the claimed method will treat cancer. If this is Applicants' intention, they must present such evidence.

In claim 41, the candidate agent is undefined, the method of combining a claim 13 compound and a candidate agent is undefined, the possible effects to be noted in a candidate agent are undefined, and potential activity of the p70S6k kinase is undefined. The indefiniteness of the term "modulator" has been considered above.

Claim 42 fails to define to whom or to what the compound is administered. The type of cell is undefined. The claim fails to define if administration is *in vivo* or *in vitro.*

In claim 43, "abnormal metabolic activity" is undefined; it can be inclusive of such diverse conditions as GPi efferent projections in parkinsonism (Eidelberg, et al., cited above), recurrent and metastatic adrenocortical carcinoma (Mackie, et al., cited above), and human breast cancer (McDermott, et al., cited above). The claim fails to define to whom or to what the compound is administered. The type of cell is undefined. The claim fails to define if administration is *in vivo* or *in vitro.*

Accordingly, claims 37 and 39-43 fail to comply with the enablement requirement of 35 U.S.C. 112, first paragraph.

Objected Claims

Claim 34 is objected to as reciting both elected and non-elected subject matter. Compound 1 in claim 34 is non-elected subject matter of Group I of the Lack of Unity set forth in the Office Action of 02-05-2009. The claims should be directed only to elected subject matter. Appropriate correction is required.

Claim 34 would be allowable if rewritten or amended to overcome the above-noted objection.

Allowed Claims

Claims 13-20, 29 and 35 are allowed. An examiner's statement of reasons for allowance can be found in the previous Office Action.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia M. Jaisle/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, AU 1624